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(54) Optic fiber probe

Optischer Lichtfaser-Messfühler

Capteur optique comprenant des fibres

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Description

Field of the Invention

[0001] The present invention relates to fiber optic probes for spectrophotometry. In particular, the present invention relates to a fiber optic probe optimized for absorbance measurement applications in fluid media where bubbles, particulate matter, measurement sensitivity, stray light rejection, and flow dynamics are a concern. The present invention further relates to automated, multi-channel spectrophotometric measurements that employ multiple fiber optic probes coupled to either multiple single-channel spectrometers, multiplexed single-channel spectrometers, or single multi-dimensional "imaging" spectrographs that employ a two-dimensional CCD (charge-coupled-device) array as the detection and measurement element.

Background of the Invention

[0002] Spectrophotometric absorbance measurements are typically performed by measuring the amount of light (I_0) that passes through subject media which contains no sample components of interest and then measuring the amount of light (I) that passes through the subject media that does contain the sample component to be measured. The quantity I_0 is referred to as the reference or blank light intensity and the quantity I is referred to as the sample intensity. The concentration of the sample component of interest is proportional to the Absorbance (A), where $A = - \mathrm{Log}_{10}(I/I_0)$.

[0003] The terms "spectrograph" and "spectrometer" are often used in reference to the same instrument type. However, a spectrograph is a special case of a spectrometer that uses a stationary grating and has no parts (other than a shutter in some cases) that move during the measurement cycle. Light is instantaneously diffracted horizontally across the surface of a multi-element array detector (CCD or photodiode). Some spectrometers use a motorized grating to scan across the spectrum and direct light through an exit slit onto a single-element detector.

[0004] When fiber optic technology is used, light from a source may be transmitted across a light path gap in the subject media by one or more transmitting fibers, and received by one or more receiving fibers which direct the transmitted light to the detection and measurement device. Probes using this approach are referred to as transmittance probes. In a variation of this basic technique, the transmitting and receiving fibers are side by side and a mirror is used to reflect light back through the subject media onto a receiving fibers. This, in effect, doubles the light path gap.

[0005] The applications of *in situ* or remote measurements using fiber optic spectrophotometric probes has increased significantly in step with advances in fiber optic technology, spectrometry and computing hardware, and data collection and processing software.

Many commercial systems now support a wide range of *in situ* spectrophotometric applications which monitor multiple signals from either multiplexed individual spectrometers or single spectrographs employing two-dimensional CCD detector arrays. Only within the last five years have these advances been applied to commercial *in situ* spectrophotometric monitoring systems targeted to pharmaceutical *in vitro* dissolution testing.

[0006] There have been minimal advances in fiber optic probe design that target the specific needs of pharmaceutical dissolution testing where flow dynamics and particulate interference are primary concerns. The maintenance of constant flow dynamics throughout an *in vitro* dissolution test is a major concern of pharmaceutical laboratories that are required by law to perform dissolution testing before allowing product dosage forms to be sold. The *in vitro* dissolution testing must be done in accord with standards and procedures defined by the U.S. Food and Drug Administration and the United States Pharmacopoeia. Published studies have shown that large diameter probes alter flow dynamics and cause observed tablet dissolution rates to be abnormally high.

[0007] Fiber optic probes used in all current commercial *in situ* dissolution testing systems are based on insertion probe designs commonly employed in industrial environments where the probe must be highly rugged and cylindrical. Typically, the transmitting and receiving fibers are side-by-side (parallel) and in the same enclosure which has a uniform diameter over the submerged portion of the probe. The uniform diameter allows the probe to be readily inserted into a reactor, flowing stream, or other vessel where a seal between the probe and vessel walls is required. A probe used for diagnosing fluid or vapor in an in situ environment is disclosed in US 5,691,701. The probe comprises light emitting and light receiving, fibers as well as a gap between them. This probe is mounted in the wall of the reservoir of a fluid to be tested and can be provided with a screen surrounding the emission and the detection fibers to prevent debris from entering the gap between the fibers.

Another probe for in situ measurements is described in US 4,699,509. This probe of a device for measuring contamination of a lubricant comprises a detector unit. The detector unit has windows for forming an optical gap, light guides, formed of optical fiber for guiding external light to the window and prisms for deflecting light by 90°. The components are received in a body, which holds the elements at a given position and which can be fixed to a vessel wall.

A probe for measuring amount of microbial cells in a liquor is know from JP-A-01187098. Bundles of optical fibers are described to be introduced into pipes. Dissolution testing and other forms of laboratory-based testing, where fluid media in a wide-mouthed, unsealed vessel is monitored, have no such requirements for extreme ruggedness or cylindrical configuration.

Objects and Summary of the Invention

[0008] Therefore, an object of the present invention is to fully meet the needs of laboratory-based, *in vitro* pharmaceutical dissolution testing and other types of laboratory testing with similar requirements.

[0009] Another object of the present invention is to provide a probe for sampling fluids which provides a direct light path between a transmitting optic fiber and a receiving optic fiber without the requirement for additional path-altering optic elements such as mirrorsor prisms.

[0010] Another object of the present invention is to provide a probe for sampling fluids which improves the optic efficiency over earlier designs and allows small-diameter optic fiber to be used to reduce flow disturbances in the sample gap area.

[0011] Yet another object of the present invention is to provide a probe for sampling fluids which reduces or eliminates probe surfaces that can trap air bubbles or accumulate debris in the sample gap.

[0012] These objects are solved by an optic fiber probe as claimed in claim 1.

[0013] The present invention is a fiber optic probe that includes an open, fine-bodied probe structure and an efficient means of transmitting source light through fluid media to one or more receiving fibers. The probe structure offers minimal resistance or disturbance to fluid flow in the sample area in particular by the use of support tubes and thus minimizes any affect on solution hydrodynamics or turbulence. The features of one embodiment of the invention are an open structure, very low probe displacement volume and surface area, a light path gap that is perpendicular to the longitudinal axis of the probe in the preferred embodiments, and an efficient means of coupling transmitted light to the receiving fiber that employs no internal optic elements or fiber end modifications. The latter feature also ensures that the invention has excellent stray-light rejection characteristics. Because of its simplicity the probe is economical to manufacture.

[0014] Elimination of a discrete light reflecting or refracting element such as a mirror or prism increases the efficiency of light throughput for a given fiber size. Thus it becomes possible to employ smaller diameter fibers than would be required when a discrete light reflecting or refracting element is present. This translates to a significant advantage over conventional designs when the present invention is coupled with a multi-channel "imaging" spectrograph based on a two-dimensional CCD array detector. Hence, the invention also relates to a multi-channel, fiber optic-based spectrometer system as claimed is claim 15.

[0015] Coupling to the spectrograph is achieved by bringing the distal ends of receiving fibers together into a vertical array bundle that is mounted to the input of a commercially available spectrograph. The spectrograph employs a fixed grating to diffract the light across the wavelength range of interest and additional optic elements to image the multiple light beams onto the surface of a two-dimensional CCD array. Example arrays are composed of 256 X 256, 512 X 512, 1024 X 1024, and other variations on detecting pixel configurations. A CCD spectrometer that could formerly support a maximum of six to eight probes using prisms and 600 μm fibers would now be able to support 12 or 18 "transverse light path" probes of the present invention design using 300 or 200 μm fibers. This translates to a significant advantage in the application of dissolution testing which is done in groups of six to eight vessels. The CCD spectrometer in the previous example would now be able to support up to three dissolution baths or experiments at the same time.

[0016] The probe of the present invention significantly reduces the cost of equipment required to automatically monitor multiple dissolution tests by elimination of expensive optic elements in the optic probe and increasing the number of channels which one spectrograph can monitor. Multi-channel instruments can monitor more probes of the current design as compared to conventional probes.

[0017] In use, one or more probes are inserted into the reference fluid media and the reference intensities are measured and recorded. If the concentrations of chemical species are to be measured, then the probes will be inserted into solutions containing a known concentration of reference standard chemical. The reference standard absorbance values will be measured and response factors calculated for each probe. These factors will be used to convert sample absorbance values into concentration values. The probes are then rinsed and inserted into the sample fluid media and monitoring of the sample intensities is performed according to the requirements of the particular application.

[0018] In the example application of pharmaceutical dissolution testing, the probes are placed into standard, wide-mouthed dissolution vessels from above the fluid media surface. Typically they are held in place by a suitable clamp or holder for the duration of the test, or they may be periodically raised above the sampling point by an automated mechanism for periods of time when measurements are not being made. The latter action may be needed to reduce effects on solution hydrodynamics produced by conventional insertion probes. The clamp that holds the probe structure must be adjustable to allow for different sampling heights that correspond to different solution volumes that may be employed during the dissolution test. The USP standard sampling point is half way between the top of the stirring element (paddle or basket) and the top of the test solution. Thus the distance from the light path gap to the vessel cover will vary depending on the solution volume. The clamp must allow the operator to properly configure the probe "sampling height" prior to starting the test.

[0019] During the course of sample measurements, bubbles may be produced as a result of liquid media deaeration. In some applications, as in pharmaceutical dis-

solution testing of dissolving tablets, particulate matter will also be present during the entire measurement period. The open structure and transverse light path of the present invention helps ensure that particulate matter and bubbles will not be trapped in the light path gap and produce erroneous absorbance measurements. The low displacement volume and surface area of the present design allows the probes to remain in the vessels for the duration of the test and obviates the need for an additional automated mechanism to raise the probes above the sampling point.

[0020] Together the different embodiments of the present invention form a family of fiber optic probe designs that can accommodate a wide range of sensitivity or light path length requirements for monitoring a variety of pharmaceutical dosage forms during dissolution tests.

Brief Description of the Drawings

[0021] These and other features, aspects and advantages of the present invention will become better understood with regard to the following description, appended claims and accompanying drawings where:

FIG. 1 is a front elevation drawing of a preferred embodiment of the present probe design showing the bent tubing structures which contains the transmitting and receiving fibers and the structural members which tie the two bent structures together and maintain fiber alignment;

FIG. 2 is a detailed front cross section of the light path gap area of the probe of FIG. 1 showing the transmitting and receiving fiber ends and a structural cross-member used to maintain alignment at the light path gap;

FIG. 3 is a front elevation drawing of an optic probe assembly comprising the optic probe of FIG. 1, and an upper support assembly for supporting the probe in a sample vessel;

FIG. 4 is a side elevation drawing of the probe assembly of FIG. 3;

FIG. 5 is a schematic drawing of a multi-channel, fiber optic-based UV spectrometer system comprising ten optic probes of the present invention connected to a single spectrograph via multiple transmitting and receiving optic fibers.

FIG. 6A is a front view of an alternative embodiment of the present invention showing an elongated tube portion and two lower curved tube portions having symmetric or mirror-image compound-curved tube portions providing a direct path light gap;

FIG. 6B is a front view of an alternative embodiment of that shown in FIG. 1 wherein the elongated body portion spreads or fans outward towards the proximal end;

FIG. 6D is a front view of an alternative embodiment of the present invention having an integral body assembly.

Description of the Preferred Embodiments

[0022] The following is a description of the preferred embodiments of a fiber optic probe for measuring fluid media and a method for automated, multi-channel spectrophotometric measurements utilizing the probe.

[0023] FIG. 1 shows a optic fiber probe 100 according to a preferred embodiment of the present invention. Probe 100 comprises an elongated body portion 101, proximate end portion 103, and distal end portion 105. In the embodiment, probe 100 comprises two support members or tubes 107A and 107B. Tubes 107A and 107B comprise elongated tube portions 109A and 109B and curved tube portions 111A and 111B.

[0024] In the preferred embodiments, elongated tube portions 109A and 1098 of elongated body portion 101 define the longitudinal axis 113 of the probe. Elongated body portion 101 allows immersion of distal end portion 105 to the desired depth below surface 115 of a sample vessel 102. Tube 107A serves as a support member for transmitting optic fiber 117A interior to tube 107A. Likewise, tube 1078 serves as a support member for receiving optic fiber 117B interior to tube 107B.

[0025] In the preferred embodiments, curved tube portion 111 A bends approximately 90 degrees toward tube 107B and curved tube portion 111B bends approximately 90 degrees toward tube portion 111A to define a sample gap 119 between respective distal tube ends 121A and 121B.

[0026] In the preferred embodiments, tubes 107A and 107B are connected by upper alignment member or cross-member 123 and lower alignment member or cross-member 125. Cross members 123 and 125 provide structural support for tubes 107A and 107B and provide alignment between optic fiber ends as shown in FIG. 2.

[0027] FIG. 2 is a detailed front view cross-section of sample gap 119 area of the optic fiber probe 100 showing optic surface 203A of transmitting optic fiber 117A supported at distal tube end 121A and optic surface 203B of receiving optic fiber 117B supported at distal tube end 121B. Lower cross member 125 supports curved tube portions 111A and 111B so that longitudinal or optic axis 205A of transmitting optic fiber 117A and longitudinal or optic axis 205B of receiving optic fiber 117B are aligned with gap width 207 between optic surface 203A and optic surface 203B. In the preferred embodiments, cross-member 125 supports curved tube end portions 111A and 111B so that longitudinal axes 205A and 205B are parallel. In the most preferred embodiments, longitudinal axes 205A and 205B are coincident.

[0028] Sample gap 119 provides a direct path for electromagnetic wave communication between transmitting optic fiber 117A and receiving optic fiber 117B, without path-altering optic elements such as mirrors or prisms. In the preferred embodiments, the electromagnetic communication is light and in the more preferred embodiments, the electromagnetic communication is UV wavelength light. Disposing the optic axis (longitudinal axis of the sample gap 119) perpendicular to longitudinal axis 113 of the probe minimizes entrapment of air bubbles or debris on surfaces of the probe in the gap area which might otherwise interfere with the electromagnetic wave communication between the optic fibers.

[0029] In the preferred embodiments, the submerged portions of support tubes 107A and 107B such as curved tube portions 111A and 111B are small diameter tubes having close fit tolerances with interior optic fibers 117A and 117B. Support tubes 107A, 107B, and tube portions 111A and 111B are selected to have a diameter as small as practical to reduce flow dynamic disturbances during tablet dissolution tests.

[0030] In the preferred embodiments, optic fibers of diameters of 200 - 600 micrometers offer a balance of adequate throughput, flexibility, minimum radius of curvature and minimum size for low flow resistance. In the more preferred embodiments, optic fibers 117A and 117B are less than 350 micrometers. A particularly preferred embodiment utilizes 200 - 300 micrometer fibers such as 300 micrometer optic fibers that efficiently transmit UV light over the wavelength range of 200 to 400 nanometers.

[0031] Submerged portions of the tubes must provide adequate strength and support for the fibers with minimum outside diameter for reduced effects on fluid flow in the sample vessel and in the sample area. In the preferred embodiments, support tube members 107A and 107B are 16- 24 gauge stainless steel tubing. In the more preferred embodiments, support tubes 107A and 107B are 22 gauge (0,07112 cm OD, 0.04064 cm (D), 0.028" OD, 0.016" ID) type 316WSS hypo tubing, standard wall. In the preferred embodiments, the support tube diameter 210 of the submerged tube portions such as elongated body portion 101 and distal end portion 105 is less than 2.0 mm in order to reduce fluid flow effects in the vessel and sample area. In the more preferred embodiments, the support tube diameter of the submerged portions is less than 1.5 mm. In the most preferred embodiments, the support tube diameter at the distal end portion 105 is less than 1.0 mm.

[0032] In the preferred embodiments, the support tube diameter at the distal end portion 105 is less than 0.05 of probe length 131 to reduce fluid flow effects in the active sample area. In the more preferred embodiments, the support tube diameter at the distal end portion 105 is less than 0.02 of probe length 131. In the most preferred embodiments, the support tube diameter at the distal end portion 105 is less than 0.01 of probe length 131.

[0033] Reduction of the displaced volume of the submerged portions of the probe also reduces flow disturbances resulting from the probe. In the preferred embodiments, the displaced volume of the submerged portion of probe 100 is less than 200 cubic millimeters. In the more preferred embodiments, the displaced volume of probe 100 is less than 100 cubic millimeters. In the most preferred embodiments, the displaced volume of probe 100 is less than 50 cubic millimeters. The displaced volume of the submerged portion of support tubes 107A and 107B is defined as the volume of the portions of probe 100 of FIG. 1 below surface 115 when the probe is positioned in a vessel for dissolution testing purposes.

[0034] It is understood that modifications to the embodiments shown, such as non-circular tube cross-sections may be used which are within the scope of the invention. For non-circular cross sections, the effective diameter of the non-circular section is defined as:

$$D(\text{eff}) = \sqrt{1.273 \times A}$$

Where A is the cross-sectional area of the non-circular cross-section.

[0035] In the preferred embodiments, the effective diameter of lower cross-member 125 is dimensioned to the same criteria of support tube diameter 210 at distal end 105 to reduce flow disturbances and to reduce surface area in the sample gap region that would collect residue and bubbles during tablet dissolution events. In the preferred embodiments, no optic elements such as prisms or mirrors are utilized, for example, to produce multiple light path directions in the sample gap area. Such elements increase flow disturbances and increase surface area which might accumulate debris and bubbles during sampling evolutions. A direct light path as shown in FIG. 2 provides a light-efficient gap, allowing small-diameter fibers and support tubes to be used to decrease flow disturbances in the sample gap and surrounding area of the vessel.

[0036] FIG. 3 is a front elevation drawing of an optic probe assembly 300 inserted into sample vessel 302. Probe assembly 300 comprises an upper support assembly 301 fixed to an optic probe portion such as optic probe 100 of FIG. 1. Upper support assembly 301 comprises connection tubes 303A and 303B that fit over support tube members 107A and 107B of proximate end portion 103 of FIG. 1.

[0037] Connection tubes 303A and 303B comprises bend portions 305A and 305B which provide offset handle portions 307A and 3307B. Handle portions 307A and 307B comprise optic fiber connectors 309A and 309B for connecting optic fibers 311A and 311B from the instrumentation to optic fibers 117A and 117B of optic probe section 100. Probe clamp 315 of vessel cover 317 clamps probe assembly 300 and allows adjustment such as sampling height 319 of sample gap 119. Paddle assembly 321 and shaft 323, shown in phantom lines, provides

desired fluid agitation in vessel 302.

[0038] Fig 4 is a side elevation drawing of optic probe assembly 300 in vessel 302. Bend portions 305A and 305B provide offset handle portion 307A and 307B to assist in inserting, withdrawing and adjusting the position of the probe within sample vessel 302.

[0039] Bend portions 305A and 305B also minimize possible interferences with paddle drive components that are part of commercial test equipment.

[0040] In assembling of the preferred embodiments, a length of fiber (longer than the total length of the support tube member) is inserted into the curved tube portion and epoxied into place at the light path gap end. The fiber end may be either flush with the tube end or slightly extended with epoxy around the edges forming a sloping mound around the exposed fiber.

[0041] The preferred assembly method results in a polished fiber end that is flush with the tube end. The fiber end may be polished before or after inserting the fiber into the tubing. The preferred assembly procedure is to insert a length of fiber into the distal end of the tube. For large (greater than 5 mm.) sample gaps, the distal fiber end can be polished after being epoxied into place. For smaller sample gaps, the distal fiber end can be pre-polished before inserting into the distal end of the tube. If the distal fiber end is polished after insertion, the fiber may be inserted at either the proximal or distal ends. The objective is to avoid damaging the distal fiber end.

[0042] The tubes of upper support assembly 301 are inserted over the fibers and attached to the elongated tube portions of probe 100 with epoxy. The upper fiber ends are prepared for termination in the SMA connector. These fiber-to-connector termination procedures, though non-trivial, are well known and routinely employed in the telecommunications industry. The SMA (or other) connector is inserted over the fiber and attached to the upper support assembly with epoxy. Epoxy is also applied inside the ferrule. The epoxy is allowed to dry and the final polish is applied to the SMA terminated fiber.

[0043] In other embodiments and assembly procedures, no connectors are used at the probe and the fibers are terminated at the spectrograph and the light source.

[0044] In the preferred embodiments, an adjustable probe holder or clamp 315, inserted in aperture or slot 317A of vessel cover 317 secures probe assembly 300 to vessel cover 317. Probe assembly 300 is secured by clamp screw 325 and nut 327 to grip connection tubes 303A and 303B, and provide a means to adjust the sample gap depth 319 in sample vessel 302. Vessel cover 317 comprises slot 317B for insertion of shaft 323 of paddle assembly 321. The operator will adjust he holder position depending on dissolution bath type, solution volume and vessel size.

[0045] Adhesives such as epoxy may be used to fix connection tubes 303A and 303B of upper support assembly 501 to optic probe section 100 at tube ends 331. Alternatively, welding or mechanical fasteners may fix upper support assembly 501 to optic probe section 100. Adhesives such as epoxies may also secure optic fibers 117A and 117B in tube members 107A and 107B at tube end 333. Adhesives such as epoxies may be used to secure optic fibers 311A and 311B in tubes 303A and 303B of upper support assembly 501. Optic connector 509 may be an optic connector known in the art such as an SMA type connector.

[0046] FIG. 5 is a schematic diagram of a multi-channel, fiber optic-based UV spectrometer system 501 optimized for measuring the dissolution rates of pharmaceutical dosage forms. The basic measurement principle is identical to conventional UV spectroscopy, wherein dissolved component concentrations are proportional to the amount of light absorbed by the sample.

[0047] Multiple fiber optic probes, such as fiber optic probe 300 are illuminated with UV light through transmitting optic fibers 311A terminated at a low-noise deuterium light source 511.

[0048] Light passing through the sample gap 119 of probe 300 passes through receiving optic fibers 311B terminated at the inlet slit 518 to spectrograph 519. The spectrograph separates light into different wavelengths and simultaneously images the light beams onto a charge coupled device (CCD) detector.

[0049] Light intensity data is transferred to the computer 521, where software calculates and displays absorbance values and percent dissolved for each channel at user-selected time points and wavelengths. Controller 523 interfaces with computer 521 and provides control of light source 511 and spectrograph 519. Paddle assembly 321 provides desired agitation in vessel 302 as described previously. The lower end of the shaft is threaded to accept baskets and tablet dies used for intrinsic dissolution testing.

[0050] Ten or more vessels can be monitored simultaneously by coupling receiving fibers 311B to the CCD of spectrograph 519. Coupling ten or more probes such as probe 300 to a single CCD of a spectrograph is made possible by the efficient direct light path in sample gap 119 of probe 300. The direct light path allows small-diameter receiving fibers and hence a higher density of receiving fibers scanned by the CCD of spectrograph 519 than would be possible utilizing conventional probes utilizing additional optic elements such as mirrors, prisms, etc. The actual image acquisition time depends on the user-selected exposure or integration time (typically 100 - 1000 ms). In another preferred embodiment, at least 12 receiving fibers from sample vessels are monitored by a single spectrograph. In still another embodiment, at least 18 receiving fibers from sample vessels are monitored by a single spectrograph.

[0051] At each user-selected time point, the system software acquires and saves complete UV spectra for all configured channels. The collected data at a given time point is referred to as a "data set". The effect of different analytical wavelengths and/or baseline correction techniques can be immediately observed by changing the desired parameters.

[0052] Reference blank intensity spectra are acquired for both sample and standard blank solutions prior to the dissolution test. Prior to all image acquisitions the software automatically acquires a background or "dark current" reading that is subtracted from the light intensity reading. Since the background reading also contains a room light component, all light intensity and absorbance values are also corrected for any room light that may be entering through the fiber optic probes. The actual time required to acquire the background and sample intensities and transfer the data to the computer is typically 8 - 15 sec. This represents the minimum time between sample measurements.

[0053] Percent dissolved calculations are based on measurements of standard solutions and the expected amount of the target ingredient in the sample. The software has different options for correcting both sample and standard absorbance values for baseline variations related to turbidity, source drift, or light scattering.

[0054] FIGS. 6A, 6B, 6D show alternative embodiments of optic probes which reduce hydraulic flow disturbances in a sample gap portion of the probe. In each of these embodiments, the longitudinal axis of the probe is defined by the elongated body portion of the probe. The longitudinal axis of the probe will normally be perpendicular to the surface of the fluid in a sample vessel.

[0055] The elongated tube portion 609A of probe 600A comprises two elongated tubes 607A1 and 607A2, attached by welding, adhesives or mechanical fasteners. Tube portions 607A1 and 607A2 support optic fibers 617A1 and 617A2. Curved tube portions 611A1 and 611A2 comprise compound, "C" or "S" type bends to form sample gap 619A of length 633A perpendicular to longitudinal axis 613A. The curved tube portions may be symmetric as shown, or they may be non-symmetric. The diameter of lower curved tube portions 611A1 and 611A2 are small as compared to probe length 631A and follow the absolute dimensions as discussed in embodiment 100 of the optic probe to reduce hydraulic flow disturbances of the sample fluid, for example during tablet dissolution testing.

[0056] FIG. 6B shows a variation 600B of embodiment 100 of the optic probe wherein elongated tube portions 609B1 and 609B2 of support tube members 607B1 and 607B2 are angled or "fanned" outward with respect to each other and longitudinal axis 613B from the distal to the proximal end of the probe. The angling out of the proximal ends of the elongated tube portions allows curved tube portions 611B1 and 611B2 to be less than 90 degrees, improving light transmission efficiency of the optic fibers. In other embodiments, only one elongated tube portion is angled out with respect to longitudinal axis 613B. In the preferred embodiments, sample gap 619B, of length 633B, is perpendicular to longitudinal axis 613B. The diameter of lower curved tube portions 611B1 and 611B2 are small as compared to probe length 631B and consistent with absolute dimensions as discussed in embodiment 100 of the optic probe to reduce hydraulic flow disturbances of the fluid, for example during tablet dissolution testing.

[0057] FIG. 6D is an embodiment 600D of the optic probe similar to that of FIG. 6A except that elongated body portion 601D and extended leg portions 611D1 and 611D2 form an integral body assembly 641. Sample gap 619D, of length 633D, is perpendicular to longitudinal axis 613D. The diameter of extended leg portions 611D1 and 611D2 are small as compared to probe length 631D and consistent with absolute dimensions as discussed in embodiment 100 of the optic probe to reduce hydraulic flow disturbances of the fluid, for example during tablet dissolution testing.

[0058] In the preferred embodiments, a length of fiber (longer than total length of the support tube member) is inserted into the bent leg and epoxied into place at the light path gap end. The fiber end may be either flush with the tube end or slightly extended with epoxy around the edges forming a sloping mound around the exposed fiber. The fiber is then polished. This is repeated for both legs.

[0059] The tubes of upper support assembly 301of FIG. 3 are inserted over the fibers and attached to the elongated tube portions of probe 100 with epoxy. The upper fiber ends are prepared for termination in the SMA connector. These fiber-to-connector termination procedures, though non-trivial, are well known and routinely employed in the telecommunications industry. The SMA (or other) connector is inserted over the fiber and attached to the upper support assembly with epoxy. Epoxy is also applied inside the ferrule. The epoxy is allowed to dry and the final polish is applied to the SMA terminated fiber. In other embodiments, the fibers are jacketed with flexible material routinely employed in the art and terminated using industry standard connectors directly to the light source and detector.

[0060] Other embodiments of the optic probe may utilize multiple transmitting or receiving optic fibers. Yet other embodiments may utilize relatively larger diameter receiving optic fibers, and its support tube in relation to the transmitting optic fibers and its support tube. For example, in the embodiment of FIG. 6C, fiber 617C2 may be selected as the receiving fiber and be a larger diameter fiber than transmitting fiber 617C1 in order to supply a larger amount of light energy at sample gap 619C. The higher light efficiency of sample gap 619C allows a smaller diameter fiber 617C1 and a relatively small bending radius of lower tube portion 611C1. Upper support assemblies, such as that shown in FIG. 5, may be utilized with these or equivalent probes, modified as required.

[0061] Accordingly, the reader will see that the fiber optic probe of the present invention provides an *in vitro* pharmaceutical dissolution testing optic fiber probe which improves performance and consistency of tablet dissolution testing. The device provides the following additional advantages:

- The probe utilizes a direct light path without redirect-

ing the light path with mirrors, prisms or other supplementary optic elements;

- The probe reduced-diameter transmitting and receiving optic fibers allowed by the increase in optic efficiency of the direct light path gap, allows reduced-diameter probe components such as fiber support tubes and reduced hydraulic disturbances resulting from the smaller probe elements;
- The reduced-diameter receiving fibers allow more channels of sample probes analyzed by a single CCD of a spectrograph; and
- The optic probes and dissolution test systems are simple and low in cost.

[0062] Although the description above contains many specifications, these should not be construed as limiting the scope of the invention but merely providing illustrations of some of the presently preferred embodiments of this invention. Thus the scope of the invention should be determined by the appended claims and their legal equivalents, rather than by the examples given.

Claims

1. An optic fiber probe [100] for sampling fluids in a sample vessel [102], the probe comprising:

an elongated body portion [101]with a first support tube [107A] and a second support tube [107B] with a distal end portion [105] defined by a first substantially ninety degree curved tube portion [111A] and a second substantially ninety degree curved tube portion [111B] insertable in the sample vessel, the elongated body portion defining a longitudinal axis [113] of the probe;
a first optic fiber [117A] internal to the first support tube [107A], a distal end of the first optic fiber [117A] defining a first optic surface [203A] at a first distal end [121A] of the first curved tube portion [111 A];
a second optic fiber [117B] internal to the second support tube [1078], a distal end of the second optic fiber [117B] defining a second optic surface [203B] at a second distal end [121B] of the second curved tube portion [111B];
the first support tube [107A] and the second support tube [107B] spaced apart by a first cross member [123] and the first curved tube portion [111A] and the second curved tube portion [111B] connected by a second cross-member [125], the second cross member being generally arch-shaped and connected at the first distal end [121A] and the second distal end [121B], whereby a first optic axis [205A] of the first optic fiber [117A] at the first optic surface [203A] and a second optic axis [205B] of the second optic fiber [117B] at the second optic surface [203B] are generally coincident and define a longitudinal axis of a sample gap [119] at the distal end portion [105] of the probe between the first optic surface [203A] and the second optic surface [203B] for direct ultraviolet light wave communication between the first optic surface [203A] and the second optic surface [203B];
the longitudinal axis of the sample gap [119] being generally perpendicular to the longitudinal axis [113] of the probe [100].

2. The probe of claim 1 wherein the first tube [107A] and the second tube [107B] each comprise an elongated tube portion [109A, 109B] generally aligned with the longitudinal axis [113] of the probe [100].

3. The probe of claim 1 wherein the first tube [107A] comprises an inner diameter selected to provide a loose tolerance fit with the first optic fiber [117A].

4. The probe of claim 1 wherein the first tube [107A] comprises an inner diameter selected to provide a loose tolerance fit with the first optic fiber [117A] and the second tube [107B] comprises an inner diameter selected to provide a loose tolerance fit with the second optic fiber [117B]

5. The probe of claim 1 wherein the first tube [107A] and the second tube [107B] are made of stainless steel.

6. The probe [600A] of claim 1 wherein the first cross member comprises a weld portion connecting the first tube [607A1] and the second tube [607A2].

7. The probe of claim 1 wherein the first support member [107A] and the second support member [107B] disposed on the distal end portion [105] of the elongated body portion [101] comprise a predetermined diameter less than 2.0 mm and sufficiently small wherein flow disturbance presented to a fluid sample in a vicinity of the sample gap [119] does not unduly interfere with fluid flow associated with tablet dissolution in the sample fluid.

8. The probe of claim 7 wherein the probe [100] comprises a probe length [131] along an axis parallel to the longitudinal axis [113] and the predetermined diameter is less than .05 of the probe length [131].

9. The probe of claim 7 wherein the probe [100] comprises a probe length [131] along an axis parallel to the longitudinal axis [113] and the predetermined diameter is less than .02 of the probe length [131].

10. The probe of claim 7 wherein predetermined diameter is less than 1.5 mm.

11. The probe of claim 7 wherein predetermined diameter is less than 1.0 mm.

12. The probe of claim 7 wherein a predetermined submerged displacement volume of the probe is less than 200 cubic millimeters.

13. The probe of claim 7 wherein a predetermined submerged displacement volume of the probe is less than 100 cubic millimeters.

14. The probe of claim 7 wherein a predetermined submerged displacement volume of the probe is less than 50 cubic millimeters.

15. A multi-channel, fiber optic-based spectrometer system [501] for measuring the dissolution rates of pharmaceutical dosage forms comprising:

at least ten fiber optic probes [300], each of said at least ten fiber optic probes comprising an elongated body portion [101] according to one of the claims 1 through 14, a transmitting optic fiber [311A] and a single receiving optic fiber [311B], a transmitting optic fiber end surface [203A] and a receiving optic fiber end surface [203B] axially aligned and spaced to define a sample gap [119] generally perpendicular to the longitudinal axis [113] of the optic probe and comprising a direct light path between the transmitting optic fiber end surface [203A] and the receiving optic fiber end surface [203B]; and
a means for connecting said at least ten fiber optic probes to a single light source [511] and a single spectrograph [518] comprising a charged coupled device.

Patentansprüche

1. Faseroptische Sonde [100] zum Abtasten von Fluiden in einem Probengefäß [102], wobei die Sonde umfaßt:

einen langgestreckten Körperteil [101] mit einem ersten Stützrohr [107A] und einem zweiten Stützrohr [107B] mit einem distalen Endteil [105], der durch einen ersten, im Wesentlichen in neunzig Grad gekrümmten Rohrteil [111A] und einen zweiten, im Wesentlichen in neunzig Grad gekrümmten Rohrteil [111B] festgelegt ist, der in das Probengefäß einsetzbar ist, wobei der langgestreckte Körperteil eine Längsachse [113] der Sonde festlegt;
eine erste optische Faser [117A] innerhalb des ersten Stützrohrs [107A], wobei ein distales Ende der ersten optischen Faser [117A] eine erste optische Oberfläche [203A] an einem ersten distalen Ende [121A] des ersten gekrümmten Rohrteils [111A] festlegt;
eine zweite optische Faser [117B] innerhalb des zweiten Stützrohrs [107B], wobei ein distales Ende der zweiten optischen Faser [117B] eine zweite optische Oberfläche [203B] an einem zweiten distalen Ende [121B] des zweiten gekrümmten Rohrteils [111B] festlegt;
wobei das erste Stützrohr [107A] und das zweite Stützrohr [107B] durch ein erstes Querelement [123] beabstandet sind und der erste gekrümmte Rohrteil [111A] und der zweite gekrümmte Rohrteil [111B] durch ein zweites Querelement [125] verbunden sind, wobei das zweite Querelement im Allgemeinen bogenförmig ist und am ersten distalen Ende [121A] und am zweiten distalen Ende [121B] verbunden ist, wobei eine erste optische Achse [205A] der ersten optischen Faser [117A] an der ersten optischen Oberfläche [203A] und eine zweite optische Achse [205B] der zweiten optischen Faser [117B] an der zweiten optischen Oberfläche [203B] im allgemeinen zusammenfallen und eine Längsachse eines Probenspalts [119] am distalen Endteil [105] der Sonde zwischen der ersten optischen Oberfläche [203A] und der zweiten optischen Oberfläche [203B] für eine direkte Ultraviolettlichtwellen-Übertragung zwischen der ersten optischen Oberfläche [203A] und der zweiten optischen Oberfläche [203B] festlegen;
wobei die Längsachse des Probenspalts [119] zur Längsachse [113] der Sonde [100] im allgemeinen senkrecht ist.

2. Sonde nach Anspruch 1, wobei das erste Rohr [107A] und das zweite Rohr [107B] jeweils einen langgestreckten Rohrteil [109A, 109B] umfassen, die im allgemeinen auf die Längsachse [113] der Sonde [100] ausgerichtet sind.

3. Sonde nach Anspruch 1, wobei das erste Rohr [107A] einen Innendurchmesser aufweist, der so ausgewählt ist, daß eine lockere Spielpassung mit der ersten optischen Faser [117A] bereitgestellt wird.

4. Sonde nach Anspruch 1, wobei das erste Rohr [107A] einen Innendurchmesser umfaßt, der so ausgewählt ist, daß eine lockere Spielpassung mit der ersten optischen Faser [117A] bereitgestellt wird, und das zweite Rohr [107B] einen Innendurchmesser umfaßt, der so ausgewählt ist, daß eine lockere Spielpassung mit der zweiten optischen Faser [117B] bereitgestellt wird.

5. Sonde nach Anspruch 1, wobei das erste Rohr [107A] und das zweite Rohr [107B] aus rostfreiem Stahl bestehen.

6. Sonde [600A] nach Anspruch 1, wobei das erste Querelement einen Schweißteil umfaßt, der das erste Rohr [607A1] und das zweite Rohr [607A2] verbindet.

7. Sonde nach Anspruch 1, wobei das erste Stützelement [107A] und das zweite Stützelement [1078], die am distalen Endteil [105] des langgestreckten Körperteils [101] angeordnet sind, einen vorbestimmten Durchmesser umfassen, der geringer als 2,0 mm und ausreichend klein ist, wobei eine Strömungsstörung, die einer Fluidprobe in einer Nähe des Probenspalts [119] präsentiert wird, die Fluidströmung, die einer Tablettenauflösung in dem Probenfluid zugeordnet ist, nicht übermäßig stört.

8. Sonde nach Anspruch 7, wobei die Sonde [100] eine Sondenlänge [131] entlang einer zur Längsachse [113] parallelen Achse umfaßt und der vorbestimmte Durchmesser geringer ist als 0,05 der Sondenlänge [131]

9. Sonde nach Anspruch 7, wobei die Sonde [100] eine Sondenlänge [131] entlang einer zur Längsachse [113] parallelen Achse umfaßt und der vorbestimmte Durchmesser geringer ist als 0,02 der Sondenlänge [131].

10. Sonde nach Anspruch 7, wobei der vorbestimmte Durchmesser geringer ist als 1,5 mm.

11. Sonde nach Anspruch 7, wobei der vorbestimmte Durchmesser geringer ist als 1,0 mm.

12. Sonde nach Anspruch 7, wobei ein vorbestimmtes Eintauch-Verdrängungsvolumen der Sonde geringer ist als 200 Kubikmillimeter.

13. Sonde nach Anspruch 7, wobei ein vorbestimmtes Eintauch-Verdrängungsvolumen der Sonde geringer ist als 100 Kubikmillimeter.

14. Sonde nach Anspruch 7, wobei ein vorbestimmtes Eintauch-Verdrängungsvolumen der Sonde geringer ist als 50 Kubikmillimeter.

15. Mehrkanal-Spektrometersystem [501] auf Faseroptikbasis zum Messen der Auflösungsraten von pharmazeutischen Dosierungsformen, umfassend:

mindestens zehn faseroptische Sonden [300], wobei jede der mindestens zehn faseroptischen Sonden einen langgestreckten Körperteil [101] nach einem der Ansprüche 1 bis 14, eine optische Sendefaser [311A] und eine einzelne optische Empfangsfaser [311B] umfaßt, wobei eine optische Sendefaser-Stirnfläche [203A] und eine optische Empfangsfaser-Stirnfläche [203B] axial ausgerichtet und beabstandet sind, um einen Probenspalt [119] festzulegen, der zur Längsachse [113] der optischen Sonde im Allgemeinen senkrecht ist und einen direkten Lichtweg zwischen der optischen Sendefaser-Stirnfläche [203A] und der optischen Empfangsfaser-Stirnfläche [203B] umfaßt; und
eine Einrichtung zum Verbinden der mindestens zehn faseroptischen Sonden mit einer einzelnen Lichtquelle [511] und einem einzelnen Spektrographen [518] mit einem ladungsgekoppelten Bauelement.

Revendications

1. Capteur optique comprenant des fibres (100), pour échantillonner des fluides dans un récipient à échantillon (102), le capteur comprenant :

- une partie allongée de corps (101) avec un premier tube support (107A) et un deuxième tube support (107B) avec une partie d'extrémité distale (105) définie par une première partie de tube (111A) incurvée, pour l'essentiel, à quatre-vingt-dix degrés et une deuxième partie de tube (111B) incurvée, pour l'essentiel, à quatre-vingt-dix degrés pouvant s'insérer dans le récipient à échantillon, la partie allongée de corps définissant un axe longitudinal (113) du capteur ;
une première fibre optique (117A) interne au premier tube support (107A), une extrémité distale de la première fibre optique (117A) définissant une première surface optique (203A) en une première extrémité distale (121A) de la première partie incurvée de tube (111A) ;
une deuxième fibre optique (117B) interne au deuxième tube support (107B), une extrémité distale de la deuxième fibre optique (117B) définissant une deuxième surface optique (203B) en une deuxième extrémité distale (121B) de la deuxième partie incurvée de tube (111B) ;
le premier tube support (107A) et le deuxième tube support (107B) étant espacés par un premier élément transversal (123), et la première partie incurvée de tube (111A) et la deuxième partie incurvée de tube (111B) raccordées par un deuxième élément transversal (125), le deuxième élément transversal ayant une forme générale d'arche et étant raccordé à la première extrémité distale (121A) et la deuxième extrémité distale (121B), un premier axe optique (205A) de la première fibre optique (117A) à la première surface optique (203A) et un deuxième axe optique (205B) de la deuxième fibre optique (117B) à la deuxième surface optique (203B) coïncidant de façon générale et définissant un axe longitudinal d'une ouverture à échantillon

(119) à la partie d'extrémité distale (105) du capteur entre la première surface optique (203A) et la deuxième surface optique (203B) pour une communication directe d'onde de lumière ultraviolette entre la première surface optique (203A) et la deuxième surface optique (203B) ;
l'axe longitudinal de l'ouverture à échantillon (119) étant, de façon générale, perpendiculaire à l'axe longitudinal (113) du capteur (100).

2. Capteur selon la revendication 1, le premier tube (107A) et le deuxième tube (107B) comprenant chacun une partie allongée de tube (109A, 109B) alignées de façon générale avec l'axe longitudinal (113) du capteur (100).

3. Capteur selon la revendication 1, où le premier tube (107A) comprend un diamètre intérieur choisi pour fournir une adaptation à tolérance lâche à la première fibre optique (117A).

4. Capteur selon la revendication 1, où le premier tube (107A) comprend un diamètre intérieur choisi pour fournir une adaptation à tolérance lâche à la première fibre optique (117A) et où le deuxième tube (107B) comprend un diamètre intérieur choisi pour fournir une adaptation à tolérance lâche à la deuxième fibre optique (117B).

5. Capteur selon la revendication 1, où le premier tube (107A) et le deuxième tube (107B) sont fabriqués en acier inoxydable.

6. Capteur (600A) selon la revendication 1, où le premier élément transversal comprend une partie de soudage raccordant le premier tube (607A1) et le deuxième tube (607A2).

7. Capteur selon la revendication 1, où le premier élément support (107A) et le deuxième élément support (107B) disposés à la partie distale (105) de la partie allongée de corps (101) comprennent un diamètre prédéterminé inférieur à 2,0 mm et suffisamment petit, dans lequel une perturbation d'écoulement présentée par un échantillon fluide à proximité de l'ouverture à échantillon (119) ne vient pas interférer outre mesure avec l'écoulement de fluide associé à une dissolution de tablette dans le fluide échantillon.

8. Capteur selon la revendication 7, où le capteur (100) comprend une longueur de capteur (131) le long d'un axe parallèle à l'axe longitudinal (113) et le diamètre prédéterminé est inférieur à 0,05 de la longueur de capteur (131).

9. Capteur selon la revendication 7, où le capteur (100) comprend une longueur de capteur (131) le long d'un axe parallèle à l'axe longitudinal (113) et le diamètre prédéterminé est inférieur à 0,02 de la longueur de capteur (131).

10. Capteur selon la revendication 7, où le diamètre prédéterminé est inférieur à 1,5 mm.

11. Capteur selon la revendication 7, où le diamètre prédéterminé est inférieur à 1,0 mm.

12. Capteur selon la revendication 7, où un volume de déplacement submergé prédéterminé du capteur est inférieur à deux cents millimètres cube.

13. Capteur selon la revendication 7, où un volume de déplacement submergé prédéterminé du capteur est inférieur à cent millimètres cube.

14. Capteur selon la revendication 7, où un volume de déplacement submergé prédéterminé du capteur est inférieur à cinquante millimètres cube.

15. Système de spectromètre multicanal basé sur de la fibre optique (501) pour mesurer le taux de dissolution de formules de dosage pharmaceutiques comprenant :

au moins dix capteurs optiques comprenant des fibres (300), chacun desdits dix capteurs optiques comprenant des fibres comprenant une partie allongée de corps (101) selon l'une quelconque des revendications 1 à 14, une fibre optique de transmission (311A) et une fibre optique unique de réception (311B), une surface d'extrémité de fibre optique de transmission (203A) et une surface d'extrémité de fibre optique de réception (203B) alignées selon l'axe et espacées pour définir une ouverture à échantillon (119) de façon générale perpendiculaire à l'axe longitudinal (113) du capteur optique et comprenant un chemin direct de lumière entre la surface d'extrémité de fibre optique de transmission (203A) et la surface d'extrémité de fibre optique de réception (203B) ; et
un moyen pour raccorder lesdits au moins dix capteurs optiques comprenant des fibres à une unique source de lumière (511) et un unique spectrographe (518) comprenant un dispositif à couplage de charge.

FIG. 1

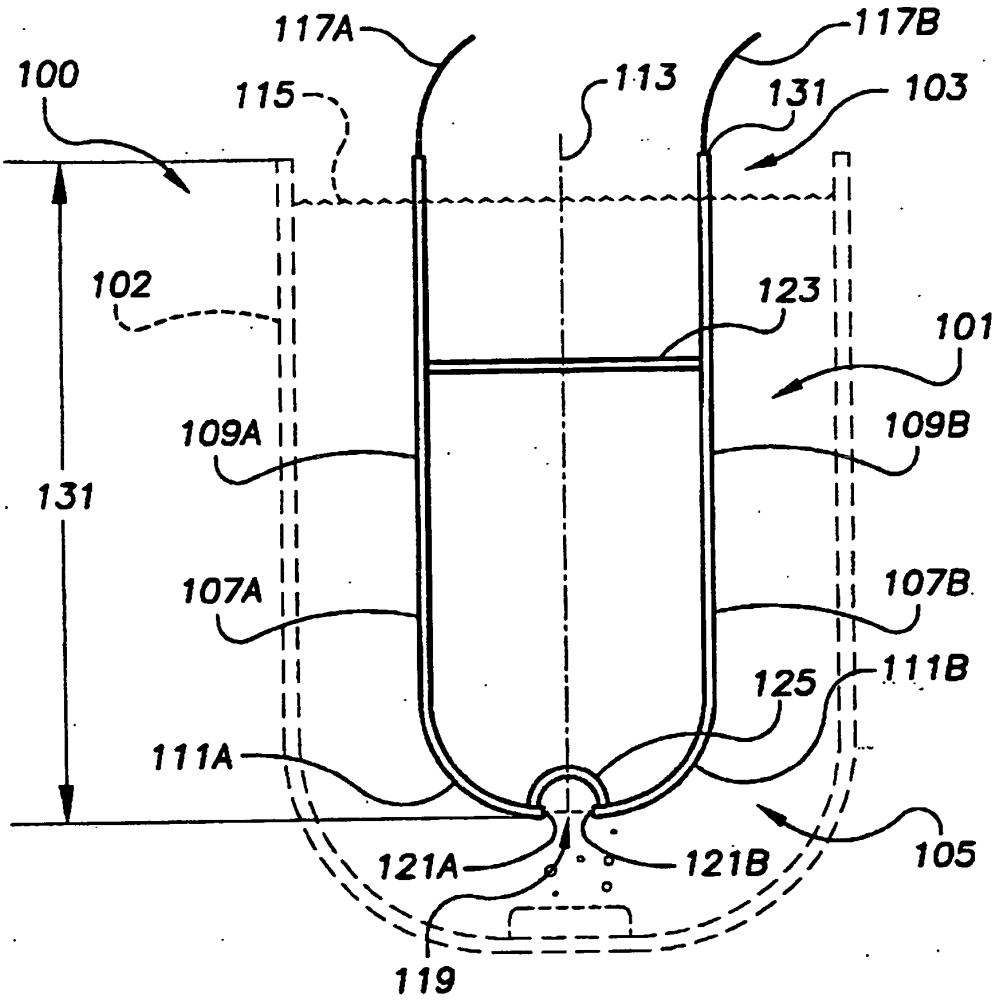

117A
117B
100
115
113
131
103
102
123
101
109A
109B
131
107A
107B
125
111B
111A
121A
121B
105
119

FIG. 2

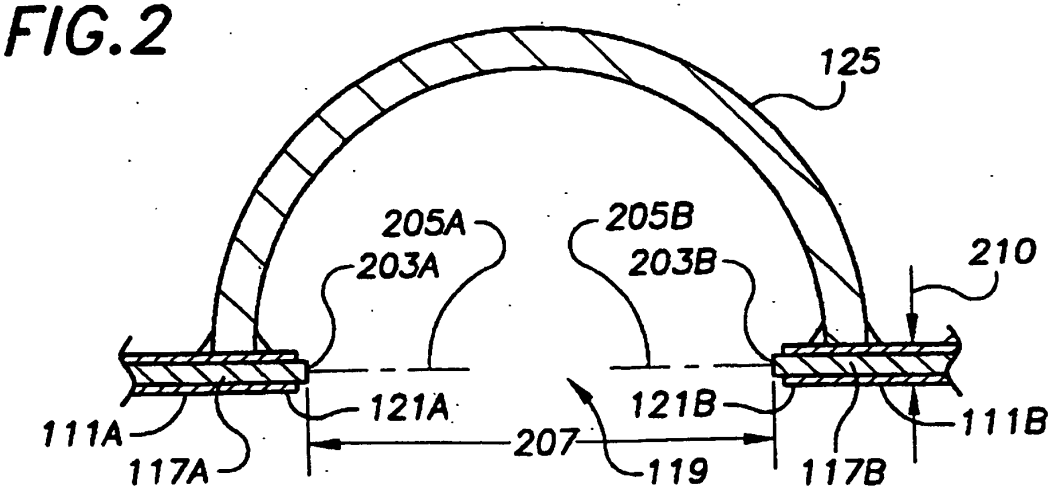

125
205A
205B
203A
203B
210
121A
121B
111A
111B
207
117A
119
117B

FIG.3

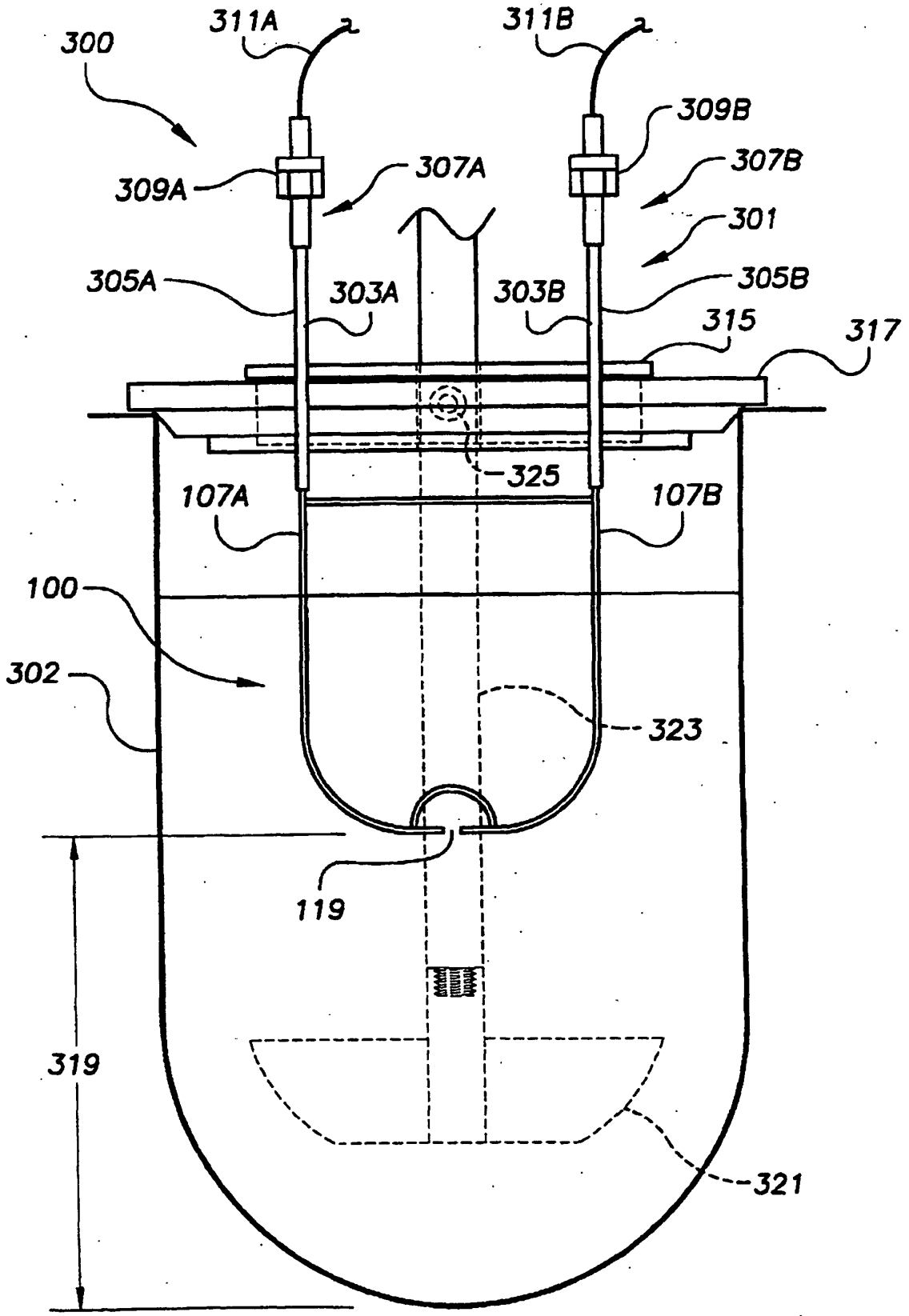

300
311A
311B
309B
309A
307A
307B
301
305A
303A
303B
305B
315
317
325
107A
107B
100
302
323
119
319
321

FIG. 4

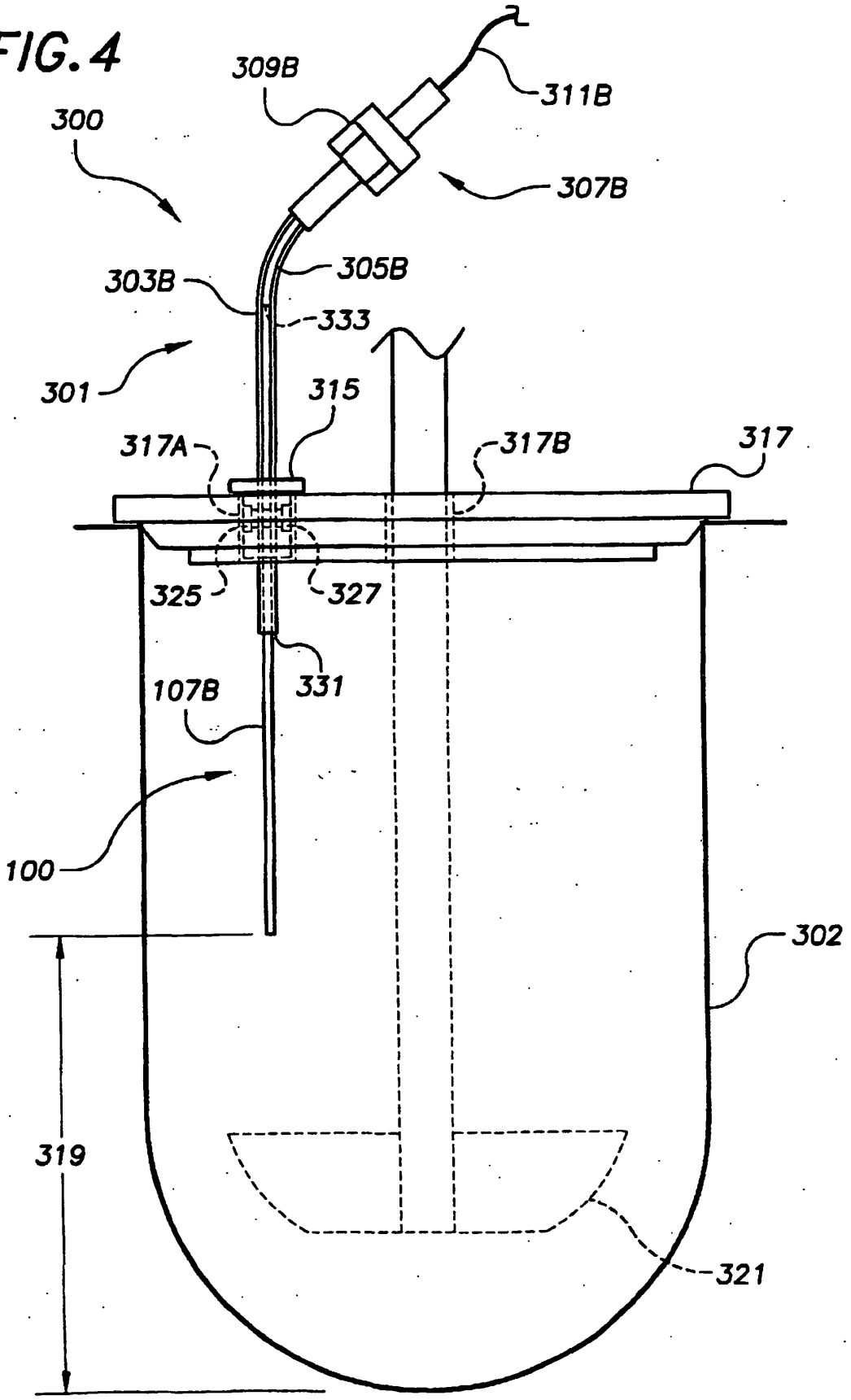

309B
311B
300
307B
303B
305B
333
301
315
317A
317B
317
325
327
331
107B
100
302
319
321

FIG.5

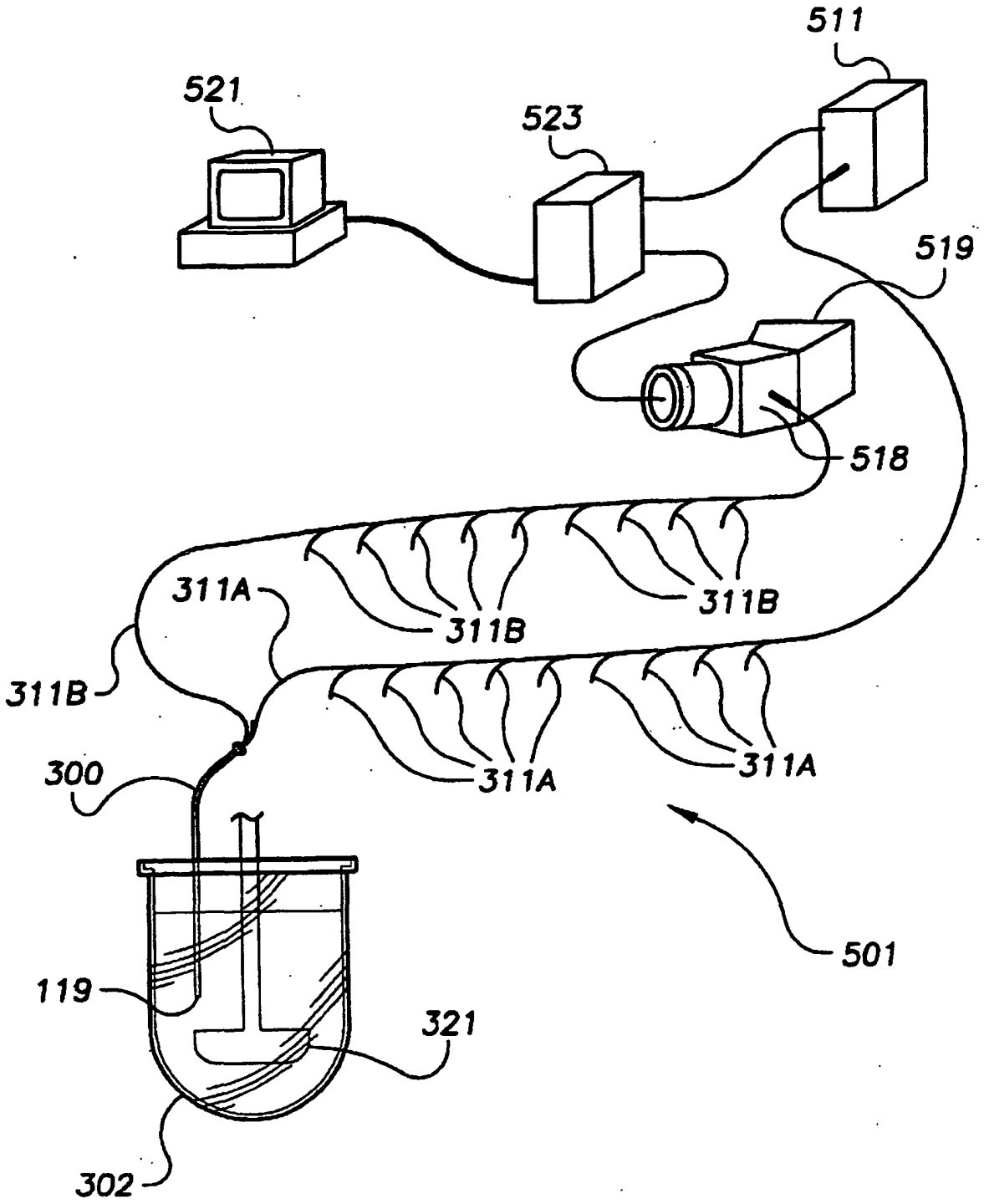

511
521
523
519
518
311A
311B
311B
311B
311B
311A
311A
300
501
119
321
302

FIG. 6B

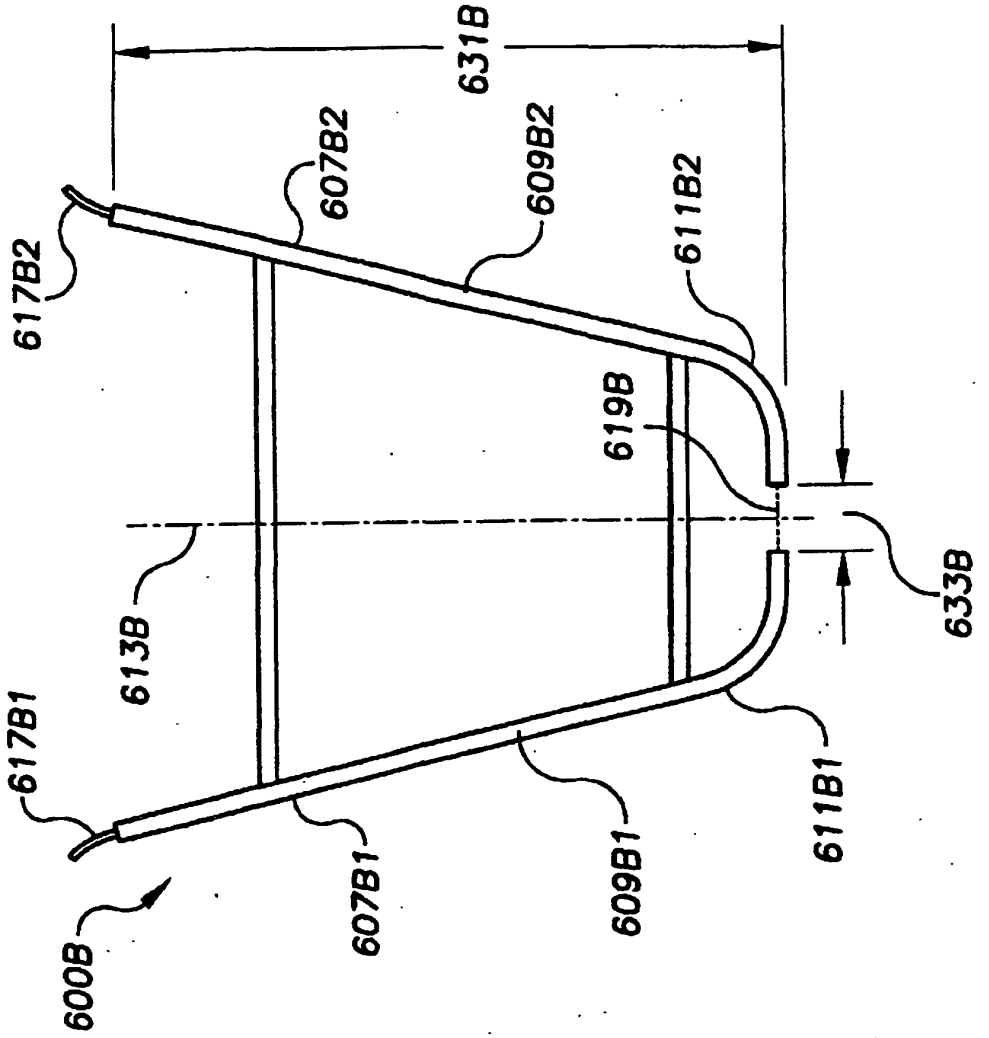

631B
607B2
609B2
611B2
617B2
619B
613B
633B
617B1
611B1
609B1
607B1
600B

FIG. 6A

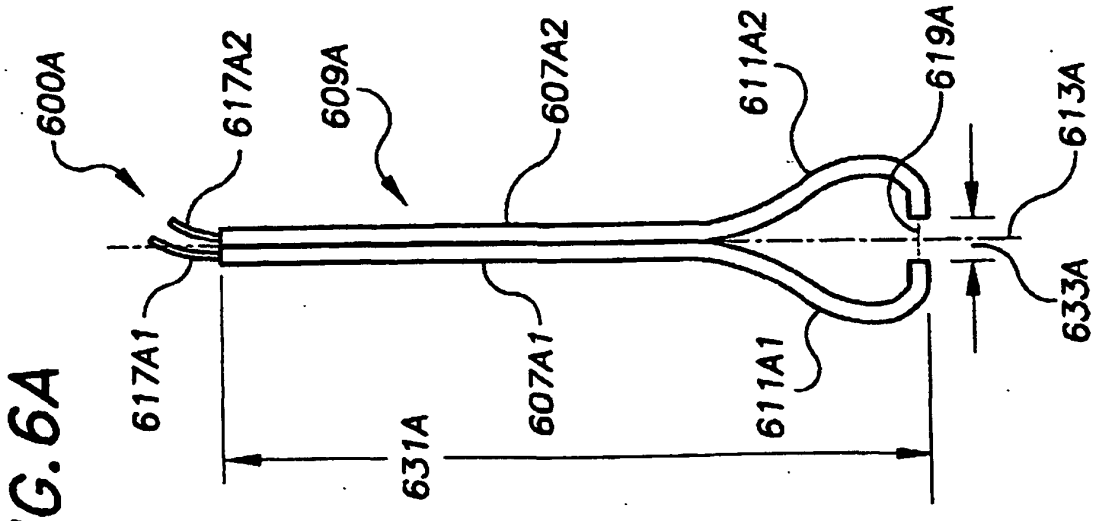
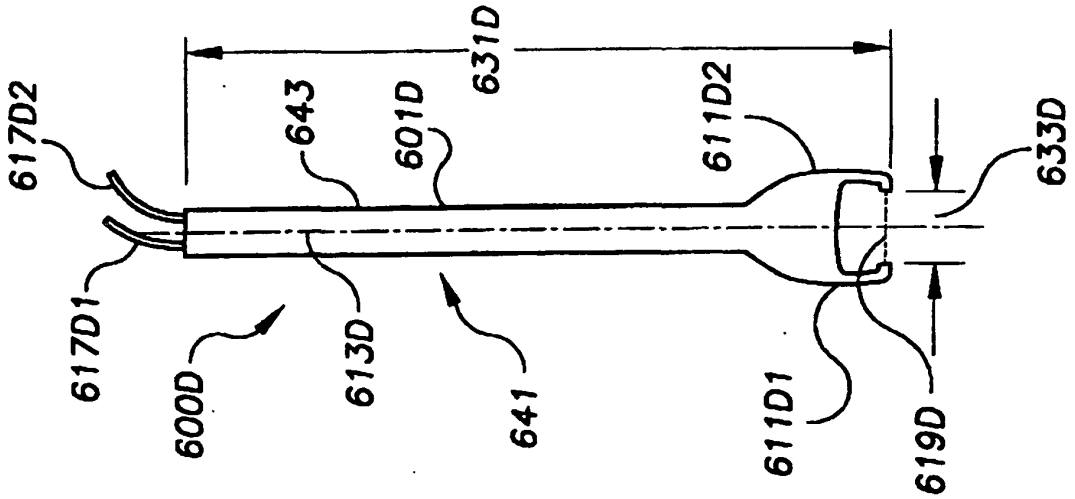

600A
617A2
609A
607A2
611A2
619A
613A
633A
617A1
607A1
611A1
631A

FIG.6D


631D
643
601D
611D2
633D
617D2
617D1
600D
613D
641
611D1
619D